Meningitis in Childhood

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Introduction and Principles of Management

In this paper the term "meningitis" is used in a clinical sense, whether the inflammatory condition is of bacterial or non-bacterial origin and whether or not it involves the brain. It covers all inflammatory disease that can be included within the terms "meningitis," "meningo-encephalitis," or "encephalitis," with the exclusion of tuberculous meningitis and poliomyelitis.

The initial signs of meningitis are usually those which indicate meningeal inflammation, but clinical signs of involvement of the brain may follow in some cases. In fatal cases evidence of cerebral damage can usually be found at necropsy. Moreover, electroencephalographic studies often show disturbance of cerebral function even without any clinical manifestations.

In pre-antibiotic days bacterial meningitis in children was usually fatal within a week to two in most cases, and the few survivors nearly always suffered severe physical and mental sequelae. Complete recovery was rare.

To-day, antibiotic treatment, if it is begun before irreparable damage has occurred, profoundly modifies the prognosis, although the difficulties of early clinical diagnosis in the youngest children remain a problem. But the success of antibiotic therapy in averting all sequelae remains in some doubt. Nyhan and Richardson (1963)—who indicate that the average mortality in various American reports is 13% and that it is higher in infancy—suggest that deafness, intellectual deficit, and personality disturbances are common sequelae in survivors. On the other hand, a recent British survey (Heycock and Noble, 1964) reports that such sequelae are rare.

Non-bacterial meningitis, for which there is no curative treatment, is usually a comparatively mild illness, although it is occasionally fatal; recent Scandinavian reports (Müller *et al.*, 1958; Nilsby, 1954) suggest that in these cases severe sequelae are also uncommon.

In order to assess the incidence of long-term sequelae, particularly those related to the central nervous system, all cases of bacterial and non-bacterial meningitis treated by one of us (D. L.) at Queen Mary's Hospital for Children, Carshalton, during 1954 to 1960 have been reviewed. Of the total of 102 cases, 64 were classified as bacterial and 38 as non-bacterial meningitis. Three children (two bacterial and one non-bacterial) had died. Of the 99 survivors, 86 were examined again in 1962, when clinical, psychological and scholastic assessments were made. E.E.G. studies were carried out in 76 cases. In Appendix A an analysis is made of the initial antibiotic treatment given in the 64 bacterial cases. Appendix B analyses the reasons for changes made in the initial "blind" antibiotic therapy.

The distinction between bacterial and non-bacterial meningitis has been made on the grounds of microbiological findings in the cerebrospinal fluid. Culture of a bacterium

is conclusive, and this was the basis of diagnosis in 52 out of 64 bacterial cases. In other bacterial cases there were several hundred polymorphs and a low C.S.F. sugar, and in very few cases did any difficulty in diagnosis arise.

The achievement of adequate levels of antibiotics in the blood and C.S.F. was regarded as a matter of extreme urgency throughout the series, and broad-range antibiotic therapy was begun without waiting for laboratory reports. In only three cases did laboratory findings indicate that the initial treatment was ineffective against the organism isolated, and in each of these an appropriate change was made within 48 hours of admission. In many cases intrathecal penicillin was given initially, but prolonged intrathecal treatment was not regarded as essential. If the child was in a state of circulatory collapse initial antibiotics were given intravenously.

Antibiotic treatment was always continued for at least one month, and for at least one week after the C.S.F. had become entirely normal. In some cases, where a slightly raised C.S.F. cell count persisted in a child who had otherwise recovered, the final stages of treatment were given at home.

Analysis of Case Histories

Clinical histories of all 102 cases were summarized and studied, and relevant details appear below.

Medical and Social History.—There was nothing notable in the medical histories of the great majority of patients who presented only a history of common childhood illnesses. Only two of the children had a history of abnormal features at birth. In four cases a mild illness had preceded the onset of meningitis by less than six weeks. In one case there had been a minor head injury within six weeks prior to the meningitis. One child had been a mental defective and an epileptic for several years before the meningitis. We defined as abnormal any environment which was either non-familial (child abandoned, etc.) or in some way antisocial (psychopathic family), or where the child was adopted or was being brought up by one parent only. In 81% of the cases the environment was classified as normal.

Age at Onset and Sex Distribution.—The age range varied from 2 months to 15 years. Fig. 1 shows that bacterial and non-bacterial meningitis differ greatly in age distribution in childhood. The proportion of boys to girls is almost exactly 2 to 1 in both the bacterial and the non-bacterial groups.

Causative organisms are shown in Fig. 2.

Number of Days Elapsing between Onset of Meningitis and Start of Treatment in the Case of Bacterial Meningitis.—Delay in diagnosis is unlikely to affect the course and prognosis of non-bacterial meningitis as there is no specific treatment for this group. On the other hand, the prognosis of untreated bacterial meningitis is almost hopeless. Early diagnosis, particularly in infancy, is both difficult and extremely important. In a minority of cases in our series there was some difficulty in judging the day on which the meningitis had begun, particularly when it followed a period of minor illness from a respiratory infection presumably due to the same infecting organism. But we are satisfied that a reasonably accurate judgment of the day of onset was made in almost

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all cases. The number of days between the appearance of symptoms and the beginning of treatment in the 64 cases of bacterial meningitis was as follows: 48 were treated within three days of onset, 6 were delayed for four days, 6 were delayed for five to eight days, and 4 were delayed for over 10 days. Three-quarters of the children, therefore, were treated with antibiotics within three days of the onset of their symptoms. Of the four cases whose admission was delayed by 10 days or more, one girl had always been an epileptic mental defective and two boys developed hydrocephalus; one of these died as a direct consequence of the meningitis. Psychological findings at follow-up further emphasize the ill-effects of delay before treatment.

FIG. 1.—Age distribution of 64 children with bacterial meningitis and of 38 with non-bacterial meningitis.

FIG. 2.—Causative organisms.

Number of Days in Hospital.—This was dependent not only on the rate of recovery but also on the quality of the home environment. The range of duration of stay in hospital varied from 3 to 122 days. The bacterial cases stayed on the whole longer (mean 48 days) than the non-bacterial ones (24 days); 27 bacterial and 4 non-bacterial cases remained in hospital for over six weeks.

Fatal Cases

Three patients died—two had bacterial and one non-bacterial meningitis.

1. **Bacterial.**—A male infant aged 14 months became febrile and ill in the afternoon and was immediately seen by the family doctor

and given a sulphonamide. The doctor was called again at 2 a.m. because the baby was unconscious and convulsing. On admission at 3 a.m. *Haemophilus influenzae* meningitis was diagnosed and treatment started. Convulsions remained uncontrollable, and the baby died at 9 a.m., within six hours of admission. Organisms cultured from the C.S.F. were sensitive to all the antibiotics given, and post-mortem examination showed meningitis with widespread cerebral damage. Despite the immediate start of treatment the baby died within 18 hours of the onset of the symptoms.

2. **Bacterial.**—A male infant aged 14 months became ill and drowsy, but was undiagnosed and untreated for 14 days before admission. He was admitted with neck rigidity, a bulging fontanelle, and left hemiplegia. *Haemophilus influenzae* meningitis was diagnosed; the C.S.F. became rapidly sterile and the sugar rose to normal on treatment, but the cell count and protein remained raised, and hydrocephalus developed. Despite intraventricular drainage and treatment the clinical condition never improved, and he died six weeks later. At post-mortem examination there was evidence of meningitis and hydrocephalus, and also a terminal staphylococcal myocarditis—an organism which had not been isolated from any other source.

3. A girl aged 3 years 5 months (non-bacterial) was admitted with a two-day history of cerebral and meningeal signs and a sterile C.S.F. typical of viral meningitis. On the third day she began to convulse and became unconscious, dying within two hours. Post-mortem findings were indicative of a generalized non-specific encephalitis.

Severity of Illness

The severity of the illness was assessed for the 99 surviving children by several criteria.

Severe Disturbance in General Health (other than specific meningeal symptoms).—This was recorded clinically at the time of the illness in 22 (35%) of the bacterial cases and in 3 (8%) of the non-bacterial cases. This difference between the two groups is statistically significant ($P=0.01$).

Disturbance of Consciousness.—In a few cases—7 (10%) bacterial and 3 (7%) non-bacterial—a severe disturbance of consciousness occurred or the patient fell into a comatose state. Mild disturbance of consciousness was recorded in 19 (30%) of the bacterial cases and in 8 (21%) of the non-bacterial cases. All the others showed no disturbance, although in babies this assessment was obviously difficult.

Clinical Anxiety.—In 13 (20%) of the bacterial cases the children did not respond to antibiotic therapy as promptly as had been hoped, and this gave rise to doubt about the suitability and efficacy of the antibiotics selected. In 5 (13%) of the non-bacterial cases natural recovery was slower than had been hoped. In all these cases “clinical anxiety” is recorded in the case histories, but this was, of course, a subjective judgment.

Altogether the clinical summaries confirm that bacterial meningitis is a more severe illness than non-bacterial meningitis.

Clinical, Psychological, Scholastic, and Electroencephalographic Assessment

For our assessment in 1962 we attempted to get each of the 99 surviving children to come with their parents to the hospital and spend half a day there for examination. Eleven of them either could not be traced or lived abroad. The parents of two more children objected on reasonable grounds to their coming for examination.

The review of those 13 cases in which parents and children did not visit the hospital in 1962 could not be as comprehensive as the reviews of the cases of the other 86 survivors, but each of the 13 cases had already been followed up for a period of one to four years after the illness; knowledge thus gained indicates that our general conclusions are unlikely to have been different if fully comprehensive reviews had been possible in all cases.

1. A clinical examination was carried out by the consultant who had been in charge of all the children during their illness.

2. *Interviews with Parents.*—Information about the family situation of each child was obtained from a discussion between the psychologist and the child's mother (usually) or the father, or, in a few cases, both parents or the guardian of the child. This discussion covered the relations of the child with his parents, friends, and teachers and also any handicaps and difficulties. All parents proved co-operative and many expressed interest in the results of the investigation. They did not appear to exaggerate or invent sequelae and only a few had been seriously worried about the possibility of long-term sequelae of the disease. In this connexion it is perhaps important to note that as all cases had been followed up by the physician for at least a year after discharge of the child from hospital most parents had been reassured at the final interview that no sequelae need be feared.

3. *Assessment of Intellectual Level.*—All but three of the children over the age of 5 were seen alone and were given an intelligence test. The Wechsler intelligence scale for children (W.I.S.C.) was chosen because of its suitability to children aged 5 to 15 and also because it covers a wide range of tasks (it includes 10 subtests). The whole of the W.I.S.C. was normally given, but in 25 cases one or more subtests had to be omitted. The 18 children who were still under the age of 5 were not easy to test in the unfamiliar environment of this investigation, and after a few attempts it was found preferable to use the Vineland maturity scales. (This is a scale by which a child's maturity can be assessed according to his ability to perform certain ordinary tasks such as climbing stairs unaided or tying his shoe-laces. The information was obtained in some cases by questioning the child's mother during the interview and in other cases by sending her a written questionnaire after the visit at the hospital. In all cases both mother and child had been seen by the psychologist.) This method of assessment is not fully reliable, but it should have enabled us to detect any backward child.

4. *School Report.*—A school report was obtained for each child at school. The head teacher or form teacher was asked to answer the following questions.

"I should be most grateful if you could let me have an account of ———'s personality and progress at your school in all fields of activity. If his/her performance varies markedly from the average in any way I should be grateful if you could describe this variation, with particular reference to the following points: (1) Level in the form. (2) Does he/she do as well as could be expected, allowing for his/her probable intellectual capacity? (3) Is this variation particularly marked in any special phase of activities, such as reading and arithmetic? (4) Are you aware of any environmental factors at home which may affect his/her progress?"

5. *Electroencephalography.*—Of the children who were clinically and psychologically examined, 76 (83%) also had an E.E.G. taken on the same day. The interpretation and classification of the E.E.G. records were carried out independently before studying the other results. The criteria of normality and abnormality of the E.E.G. were both qualitative and quantitative, and will be more fully described elsewhere. Particular attention was devoted to the presence (or absence) of rhythmic activity (including alpha rhythm) and its distribution and behaviour. The occurrence of discharges (either transient or prolonged), the excess and distribution both of irregular slow components and of fast activity, any gross asymmetries between the activities of the two hemispheres, the changes induced by simple stimuli, and the effect of hyperventilation were also studied. For the purpose of this paper a simplified grading of E.E.G. abnormality was applied, derived from the more detailed coding of individual features: A, no recognizable abnormality; B, mild or doubtful abnormality; C, definite abnormality. The purpose of carrying out E.E.G. studies so long after the meningitis was to assess the incidence of long-standing abnormalities (and their main features) in the cerebral activity and to attempt a correlation between these and clinical or psychological

anomalies. We were in no position to determine whether and how much the intervening years and any childhood illness or minor accident might have influenced the E.E.G. features.

Analysis of Results

The interval between the meningitis and our assessment for the purpose of this study varied between one and eight years. More than two-thirds of the children were seen three, four, or five years after the onset of meningitis. Three of them were seen after only one year. The mean interval between the illness and our reassessment was three years and ten months. Such sequelae as were found cannot therefore be regarded as merely temporary. The children's ages at the time of our assessment varied from 2 to 19 years, with an average age of 7 years and 10 months. Most of the children were thus of primary-school age.

Intelligence Assessment

There is no evidence that the children as a group have suffered any measurable deterioration in intelligence. The mean I.Q. of the 68 children over the age of 5 was 105 and 63% of them had an I.Q. above 100 (see Fig. 3). A similar distribution of intelligence was indicated by the results obtained by the 18 younger children on the Vineland social maturity scale. This high proportion of intelligent children may be related to the high cultural level of the suburban area from which most of our cases were drawn. It has not been possible to compare the group with a random population, but the distribution of I.Q. scores does not indicate a general lowering of intelligence level as a consequence of meningitis.

FIG. 3.—I.Q. distribution in children over 5 years old at follow-up.

Eighteen children out of the 65 who were tested on the W.I.S.C. showed a discrepancy of at least 15 points between their verbal I.Q. and their performance I.Q. scores, but there was no significant difference in the proportion of children evidencing this discrepancy in the bacterial and the non-bacterial groups. Nor was there any evidence that any of the W.I.S.C. subtests presented special difficulties for a part or the whole of our groups.

Only one of the 86 children who came for assessment was mentally defective; she had contracted a non-bacterial (vaccinal) meningitis at the age of 5 months. We had a certain amount of information about the 13 children who had not been able to come for assessment. Of these, two were considered mentally backward:

1. A girl who was a grossly retarded epileptic before the onset of bacterial meningitis; there is no evidence that her meningitis produced any further deterioration.

2. A boy in the care of a local authority who had bacterial meningitis at the age of 7 months and whose previous history was not known.

We also tried to ascertain whether any features characterizing the meningitis had any bearing on the child's subsequent intellectual level.

Of the 21 children who developed meningitis before the age of 1 year, seven had at the time of our assessment either an I.Q. level below 90 or a social maturity level below average. In comparison, only five of the 65 children who developed meningitis after the age of 1 were assessed as having an I.Q. below 90 or a social maturity level below average. This difference is statistically significant (at a level of $P=0.01$) and does not arise because most of the children who developed meningitis in infancy were bacterial cases; a comparison between the children who developed bacterial meningitis above the age of 1 and those who developed non-bacterial meningitis above that age shows no difference in the proportions of children below average intelligence. There is therefore some evidence in this series that meningitis contracted in infancy may carry a greater risk of intellectual impairment. (Of the three mental defectives described above one has always been a defective and the other two developed meningitis respectively at 6 and 7 months of age.)

Other characteristics of the illness were considered, but none was found to have any influence on intelligence level. In particular, neither the causative organism (we only compared the group who had had a meningococcus to all other groups) nor the occurrence of loss of consciousness during the illness or the length of time spent in hospital showed any relation to the subsequent intellectual level.

Emotional and Social Disturbance

In the field of personality the difficulty of comparison with the general population is even greater than in the field of intelligence. Thirty-five of the children (35% of the bacterial group and 50% of the non-bacterial group) showed some degree of disturbance at home (such as temper tantrums or intra-family tension), mild depression, anxiety, nightmares, or behaviour disturbance at school. But in only seven of these children could the symptoms be classified as severe (these include three children who came from difficult backgrounds). Neither the age of onset of meningitis nor the length of time spent in hospital, nor any of the features related to the severity of the illness, appears to have had any bearing on emotional or school difficulties.

School Progress

The progress at school of each child was classified, after a study of his or her school reports, as either "satisfactory" or "unsatisfactory." A higher proportion of children in the non-bacterial than in the bacterial group were classified as unsatisfactory (the difference being statistically significant at a level of $P=0.1$). This lower level of school performance of the non-bacterial group is *not* simply due to the fact that these were slightly older children when we assessed them. It was apparent both among the very young school-goers (aged 5 to 10) and among the slightly older ones (over 11 years old).

In 21 children of school age school performance as indicated by school reports was definitely below what would be expected from the intellectual level as assessed by our intelligence test. For example, a boy with an I.Q. of 120 was in the B stream of a secondary modern school. We found similar discrepancies in one-half of the non-bacterial group, but in less than one-quarter of the bacterial group. This difference is statistically significant at a level of $P=0.06$. This may be an important finding, as it may be related to difficulties in learning experienced by those children who had non-bacterial—that is to say, virtually untreated—meningitis. These difficulties may

not show up in ordinary intelligence tests, but if they exist they may be the source of school maladjustment and later of maladjustment at work.

General Changes Reported by Parents

Very few parents spontaneously reported any changes which might be attributed to meningitis. On direct questioning eight parents reported a variety of minor improvements (in two cases the disappearance of epileptic fits) and 12 parents mentioned a minor deterioration. In view of the common occurrence of minor personality and behaviour changes in children of the age-group under study, it is doubtful if either of these observations has any significance.

General health was usually described as good, and no important changes were reported.

Delay in walking or talking (the latter notoriously variable in a random population) was reported by the parents of 10 of the children who had developed meningitis before the age of 5. This delay had, however, been compensated in all cases.

Physical Handicaps

One little girl was completely deaf; she had contracted bacterial meningitis at the age of 5 months and was then abandoned by her parents. There is no information available about her earlier history. Three more children were reported on direct questioning to have had some hearing difficulty. Audiometric examinations showed that in none of these was the hearing defect severe enough to constitute a handicap.

Another girl was lame. She had had a non-bacterial meningitis of doubtful aetiology and was the only case in which there has been some doubt about poliomyelitis, but she had also had an accident in the months preceding her meningitis, and was living in a local-authority home.

Period Elapsing Between Onset of Bacterial Meningitis and Start of Treatment

A long delay between the appearance of symptoms and the beginning of treatment in the case of bacterial meningitis appeared to result in a more severe illness. Above we have discussed three of the four children whose admission was delayed by more than 10 days. The fourth, a boy whom we saw again at the age of 8, showed in the years following his meningitis an extremely aggressive behaviour, severe enough for his family to enlist the help of the police.

Of the six children whose admission was delayed by five, six, seven, or eight days, three had suffered temporary but severe physical or behavioural sequelae immediately after their illness. Only five of these children came for reassessment, and all but one still presented emotional, behavioural, or scholastic difficulties (tics, stammer, or marked difficulties at home)—a much higher proportion than in the rest of our group.

E.E.G. Results

Out of the 76 E.E.G. records, 16 (21%) were classified as definitely abnormal, while the others showed either no abnormality at all (21%) or only a mild abnormality (58%).

There is no difference in the proportion of definitely abnormal E.E.G. records between our bacterial and non-bacterial groups, but if we classify the cases according to their aetiology we find that all the 15 patients who had a meningococcal meningitis and had an E.E.G. at follow-up had either

a mildly abnormal (B) or a definitely abnormal (C) record. Altogether there was a larger proportion of definitely abnormal E.E.G. records in the meningococcus group than in all the other groups put together (including those of unknown cause); 40% of the meningococcus group show a definitely abnormal E.E.G. as opposed to 15% in the rest of the cases. This difference is statistically significant at a level of $P=0.1$.

The presence of an abnormal E.E.G. did not appear to be consistently related to clinical features of the original illness such as disturbance of consciousness or "clinical anxiety," to discrepancies between subtest scores in the intelligence test at follow-up, to school progress, or to emotional or social disturbance.

Discussion

Comparison of our results with those of other investigations is made difficult by the differences in age range and other characteristics of the population studied.

Our non-bacterial group has a very similar long-term prognosis to that indicated in at least two recent Scandinavian reports. Nilsby (1964) found very little difference between his patients (seen a few years after meningitis) and a control group. The patients showed a slightly lower intellectual level than the controls; moreover, like our own group, they had a less favourable school adjustment. Again, Müller *et al.* (1958) found that differences between his patients (seen a few years after non-bacterial meningitis) and his controls were minimal. His findings on the E.E.G. were similar to ours inasmuch as the proportion of abnormal records shown in the patients' group was 20% and no correlation could be clearly demonstrated between E.E.G. abnormalities and permanent clinical sequelae.

In the case of bacterial meningitis our results can be contrasted with older investigations (Wolff, 1952, and personal communication), with reports reviewed by Nyhan and Richardson (1963), and with recent Scandinavian investigations (Bergstrand *et al.*, 1957). Our conclusions about the relation between meningitis contracted in infancy and a subsequently lower intellectual level confirm Wolff's results. This probably reflects a greater tendency for brain damage to take place and learning to be affected if meningitis is contracted in infancy. However, in Wolff's group the proportion of mentally defective children is very much higher than in ours. Similarly, deafness is shown up as a sequela in a large proportion of his cases and in only one of ours.

The reasons for the great improvement in results between those previously reported in the literature and our own cannot be decided with certainty, but it seems to us most probable that three factors are involved: (1) earlier diagnosis and admission to hospital for treatment in our series; (2) longer experience in the use of antibacterial agents, and a very much wider range of such agents from which to choose; and (3) a systematic start of broad-range antibiotic therapy within a few hours of admission. These tentative conclusions would point to the extreme importance of the earliest possible diagnosis and treatment, particularly in infancy—the period of life in which early diagnosis is most difficult because the initial signs are often so vague.

It is more difficult to understand the higher incidence of mortality and severe sequelae in the various investigations reported by Nyhan and Richardson (1963). As well as possible differences in treatment, some delay before the start of treatment may well have adversely influenced the outcome and the long-term prognosis.

Finally, a comparison with the results of Bergstrand *et al.* (1957) is fruitful. They described two groups of bacterial meningitis cases, and the younger group has a much higher mortality than the other. In both groups the survivors, a few years after their meningitis, show a high proportion of

severe sequelae. The difference between the results of Bergstrand *et al.* and ours is not explainable in terms of delay before treatment (most of their cases were admitted and treated within two days) but perhaps rather in terms of a narrow range of treatment as opposed to the broad range of antibiotics used in our group.

Summary

A consecutive series of 102 children treated for meningitis and meningo-encephalitis by one physician over a period of six years (1954 to 1960) have been studied. They included 64 cases of bacterial meningitis and 38 of non-bacterial meningitis.

Bacterial meningitis was more common in younger children, while non-bacterial meningitis was distributed randomly throughout childhood.

There were three fatal cases (two bacterial, one non-bacterial). Of the 99 survivors, 86 could be traced, and they were examined again a few years after their illness, when a clinical, psychological, and scholastic assessment was made. E.E.G. studies were also carried out on 76 of them.

One child suffered from severe deafness and one was slightly lame. In neither case was the disability certainly known to be a sequela of the meningitis. There were no other physical handicaps.

The distribution of intelligence gave no evidence that either the bacterial or the non-bacterial group had suffered any measurable deterioration in intellectual level. Nor was there any indication of a high proportion of personality or behaviour disorder. The only significant difference between the bacterial and the non-bacterial groups was found in an average lower school performance of the non-bacterial. However, in many of the aspects we assessed, the non-bacterial group appeared to be at a slight disadvantage in comparison with the bacterial group.

Among those children who developed meningitis before the age of 1 year, a larger proportion (35%) had an intelligence level below average than among those who developed it later (8%).

In the case of bacterial meningitis there was striking evidence that delay in treatment of over four days (in the few cases where it occurred) was associated with severe consequences. No other characteristic of the illness appeared to have any significant bearing on the subsequent clinical and psychological state of the child.

The outcome of meningitis in this series is good. In comparison with other reported investigations the results obtained on our bacterial meningitis groups are the most striking. The methods used to ensure rapid diagnosis and the immediate institution of effective antibiotic therapy after admission to hospital are described. A broad-range combination of antibiotics was commonly used, with the result that in all but three cases subsequent bacteriological studies demonstrated that fully effective antibacterial cover had been given at once.

However, these methods would not have achieved the good results reported had the family doctors not recognized or suspected the presence of serious disease almost at once. We therefore feel that these results reflect a high professional capacity and sense of urgency among the family doctors in the area which this hospital serves.

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Appendix A

Analysis of Initial Antibiotic Therapy in 64 Consecutive Cases of Bacterial Meningitis

Penicillin and sulphafurazole	...	...	...	26
Penicillin, sulphafurazole, and streptomycin	...	...	...	13
Penicillin and streptomycin	...	...	...	8
Penicillin and tetracycline	...	...	...	1
Penicillin and sulphadiazine	...	...	...	6
Penicillin only	...	...	...	5
Chloramphenicol only	...	...	...	2
Penicillin, sulphafurazole, and tetracycline	...	...	...	1
Penicillin, sulphadiazine, and streptomycin	...	...	...	1
Streptomycin, P.A.S., and isoniazid	...	...	...	1

Treatment included	penicillin	...	...	61/64
"	"	penicillin and a sulphonamide	...	47/64
"	"	streptomycin	...	22/64
"	"	tetracycline	...	9/64
"	"	chloramphenicol	...	2/64
"	"	P.A.S. and isoniazid	...	1/64

Initial treatment with one drug only

Penicillin	...	...	5 cases (2 changed to chloramphenicol on second day. One died)
Chloramphenicol	...	...	2 cases (both changed to other effective drugs in second week to avoid toxicity)

Intrathecal treatment

None	...	...	20 cases
Penicillin one day	...	...	9 "
Penicillin 2 to 4 days	...	...	17 "
Penicillin 5 to 7 days	...	...	10 "
Penicillin 8 to 14 days	...	...	5 "
Streptomycin	...	...	2 " (1 for 1 week, 1 for 1 day)
Chloromycetin	...	...	1 case for 2 days

Appendix B

Analysis of Reasons for Changes Made in the Initial "Blind" Antibiotic Therapy

- No change** ... 38 cases
No reason was found either clinically or as a result of sensitivity studies for change in the first blind choice of single or combined antibiotic therapy. One patient died within six hours of admission before any treatment could become effective.
- Withdrawal of an antibiotic** ... 9 cases
Antibiotic treatment changed solely by the withdrawal of an antibiotic subsequently shown to be ineffective by a sensitivity test from a group of otherwise effective antibiotics.
- Toxicity** ... 4 cases
Change of antibiotics in view of toxicity or possible toxicity. The change in each case was from one effective drug to another or by the withdrawal of a toxic member of an otherwise effective group.
- Change of one agent as indicated by sensitivity tests** ... 4 cases
Change of one member of a group only, the others being already effective.
- Change of whole treatment as indicated by sensitivity tests** ... 3 cases
Change of the single antibiotic or of the whole group, none of which were effective as judged by sensitivity tests.
- Change of antibiotic on clinical grounds** ... 7 cases
In all these cases cover was already adequate as judged by sensitivity tests, and the change involved either the addition of a further effective drug or the substitute of one "effective" drug for another.

Groups 1 to 6 total 65 cases, but one case was included twice.

In groups 1, 2, 3, and 4 (a total of 54 cases, including 1 death) there was no reason, either clinically or bacteriologically, to think that the antibiotic cover was not fully effective throughout. In group 6, which contains seven cases, it is known that antibiotic cover was effective in all cases as shown by sensitivity tests, but changes were made in view of an apparently unsatisfactory initial clinical response.

There was no cause for any change on clinical grounds in any of the 12 cases in which we failed to culture an organism from the C.S.F. (usually because of previous treatment), although in Case 53 P.A.S. and isoniazid were stopped when initial doubts about the possibility of tuberculous meningitis were resolved.

Group 5, containing only three cases, is the only group in which it is known that initial therapy was probably ineffective. In all these cases, however, the change to effective antibiotic therapy, as judged by sensitivity tests, was made within the first two or three days after admission (in two cases chloramphenicol was substituted for penicillin, and in one case chloramphenicol for sulphafurazole).

Adrenal Function and the Inhibition of Allergic Responses Under Hypnosis

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Possible psychophysiological mechanisms to explain the inhibition of allergic skin reactions by direct suggestion under hypnosis (D.S.U.H.) were reviewed in the *British Medical Journal* (1964). As one possible explanation of these phenomena it was suggested that "tissue permeability can be altered by adrenocortical hormones, the secretion of which is controlled by the anterior pituitary and hence governed by the hypothalamus and all nervous mechanisms working thereon." Experimental investigation in this field, using hypnosis as a research tool (Black, 1963b), has demonstrated the production by D.S.U.H. of a shift in the dose-response curve of the Prausnitz-Küstner (P.K.) reaction. This technique of inves-

tigation involves only the passive transfer of skin-sensitizing antibodies, so that effects due to hyposensitization can be eliminated and repeatable experimental conditions can be provided in the same subject. We have therefore investigated the role of adrenal function during the production of such a shift in the dose-response curve of the P.K. reaction by D.S.U.H.

Twelve experiments were performed on two female deep-trance hypnotic subjects defined as "deep-trance" according to the arbitrary classification of Black (1963a)—they were amnesic of the period of the hypnotic trance and could be psychologically regressed under hypnosis. The subjects had already responded to D.S.U.H. with a shift in the dose-response curve of the P.K. reaction in previous experiments (Black, 1963b), and this was repeated in both subjects while estimations were made of the free plasma 11-hydroxycorticoids.

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